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ARTICLE REVIEW

The effect of thiamine supplementation for critically septic patient: An evidence-based case report

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Abstract

Sepsis has been accounted for various burdens worldwide, especially in critically ill patients. This could eventually lead to inflammatory response, provocation ischemia, and lactic acidosis. Several studies showed that thiamine deficiency is found in septic patients, with prevalence 20–70% in septic shock. Of these studies, thiamine deficiency could worsen patient's outcome. On the other hand, thiamine was suggested as a coenzyme which could improve the outcome of those patients. Unfortunately, the role of thiamine supplementation in septic patients is not conclusive. Thus, we conducted an evidence-based case study with research on PubMed, ProQuest, and Scopus using a search strategy focusing on randomized controlled trial (RCT) or cohort study on thiamine supplementation/level towards the outcome of critically ill patients with sepsis. We found three articles eligible for review after full-text assessment. Articles were appraised using the University of Oxford's tools for critical appraisal. It was known that all studies were good in terms of validity and applicability. This study showed that thiamine supplementation could improve lactate clearance and reduce mortality risk, moreover, thiamine deficiency could increase the risk of lactate acidosis. However, a high level of thiamine was associated with a high level of lactate in patients with liver failure. Therefore, thiamine supplementation could be recommended for critically ill patients with sepsis and normal liver function. Further research, such as RCT or systematic review and meta-analysis on thiamine supplementation for age groups to make this study more applicable.

Keywords thiamine, supplementation, sepsis

Introduction

Sepsis has been remaining as a condition which causes a lot of burdens. Unfortunately, its incidence has not declined. Although not yet defined before late of 20th century, sepsis has caused lot of morbidities and mortality, especially in era where antibiotics and supportive medicine not well-developed. American College of Chest Physicians and the Society of Critical Care Medicine (SCCM) introduced sepsis in the early 1990s in terms of systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock based on clinical and laboratory findings. These findings were focused on hemodynamic instability, sign of inflammation, and organ dysfunction. However, SCCM alongside with European Society of Intensive Care Medicine launched new article defining sepsis and related terms in February 2016. Main changes made were elimination of SIRS and severe sepsis, re-definition of sepsis as life-threatening organ dysfunction which stated from change in baseline sequential organ failure assessment (SOFA) score, caused by impairment of

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host's response against infection; septic shock was further defined by sepsis' subset causing cellular or metabolic dysfunction which is enough to increase mortality.[1]

World Health Organization (WHO) stated that there are estimated 48,900,000 cases of sepsis in 2017 which have caused 11,000,000 sepsis-related deaths and later accounted for up to 20% of global deaths. In addition, 85% of them occurred in low- to middle-income countries. Sepsis was contributed largely by diarrheal disease and lower respiratory tract infection. In addition, sepsis has been a classic problem with high burden on developing countries. Non-communicable disease such as maternal disorders also accounted for one-third of sepsis cases. Many cases were resistant to antibiotics, thus caused increased morbidity and mortality.[2]

Sepsis involves an extraordinary inflammatory response when endotoxin or exotoxin is released. Interaction between toxin and toll-like receptors (TLR) of monocytes and macrophages will release pro-inflammatory cytokines which activate complement system, coagulation pathway, and fibrinolysis inhibition. This event will also stimulate margination and rolling of polymorphic cells, release of vasoactive substances which caused pathological shunting of blood. Therefore, there will be ischemia, leading to anaerobic respiration and lactic acid production which in certain point leading to lactic acidosis.[3] This cascade could eventually lead to multiple organ failure (MOF) which linked into critical illness and chronic critical illness (CCI). CCI was later defined by Research Triangle Institute as stay in intensive care unit (ICU) for eight or more days with at least one of following conditions: (1) prolonged mechanical ventilation of >96 continuous hours; (2) tracheostomy; (3) sepsis/severe infections; (4) severe wounds; (5) multiple organ dysfunction. Patient with CCI was known to have minimal survival rate but require high cost. It is known that ICU-admitted patients in 2009 sum up to 20,000,000,000 USD in healthcare costs. More than 60% of them are diagnosed with sepsis.[4]

Thiamine or vitamin B1 is a non-lipid-soluble vitamin which plays important role in human metabolism. It is a cofactor of four enzymes (pyruvate decarboxylase, pyruvate dehydrogenase, transketolase, alpha ketoglutarate dehydrogenase) which play role in production of adenosine triphosphate (ATP) to provide energy.[5,6] Thiamine is transported with transepithelial transport on low concentrations, passed into tissues and blood with both active and passive diffusion. Up to 80% total intracellular thiamine further phosphorylated so that ions could bound to protein. Thiamine transport in some tissues is assisted by natrium ion and transcellular proton gradient. Some amount of thiamine is mainly stored temporarily in brain, heart, skeletal muscles, kidneys, and liver in amount of 25–30 mg.[5] Due to human's incapability of storing thiamine, thiamine deficiency could be easily developed among patients with low intake, alcohol consumption, increased urine output, and acute metabolic stress. This condition could be seen on patient attending surgical procedures or sepsis. There are estimated more than half patients with sepsis that shown with thiamine deficiency among admission. Thiamine deficiency could cause various problems such as cardiovascular failure, neurology disorders, and gastrointestinal mucosal problems.[6] However, thiamine could be easily found in products such as lentils, peas, rice, cereal, and wheat.[5]

Despite critical ill patients are commonly low intake and have thiamine deficiency, thiamine was proven effective in the treatment of patients in ICU. Intravenous administration of thiamine could repair lactic acidosis, cardiac dysfunction, and delirium.[6] It is also proven in animal model that thiamine deficiency on mice with sepsis was associated with greater bacterial in peritoneal fluid, improved oxidative stress and immune response.[7] In addition, several clinical trials have shown beneficial effect of thiamine supplementation on critically ill patients with sepsis.[6] However, drawbacks of thiamine supplementation on ICU patients with sepsis yet to be known. Therefore, we conducted this study with aim to determine relationship between thiamine supplementation and outcome in adult patient with sepsis superimposed on critical illness.

Clinical scenario

A 50-year-old man was transferred to the ICU with unconsciousness. He was diagnosed by sepsis, clinically severe malnutrition according to the American Society for Parenteral and Enteral Nutrition (ASPEN) criteria, and metabolic syndrome with type 2 diabetes mellitus,

uncontrolled hypertension, hypertriglyceridemia, and low level of high-dense lipoprotein (HDL)-cholesterol. He also has a declined renal function with supportive hemodialysis during the ICU stays. Albumin was low and quantitative was high. His blood lactate was 2.7 mmol/L at day 21 and blood gas analysis showed metabolic acidosis. The blood lactate kept on increasing and reached by 4.5 mmol/L at the day 24 despite on an adequate resuscitation. Patient received enteral nutrition and being poor tolerate since hyperlactatemia. Physician clinical nutrition specialist planned to give him thiamine supplementation to delivered metabolic resuscitation and to improve for both the lactate level and blood gas analysis profile. Thus, the support evidence was considered to this patient.

Clinical question

The inclusion criteria in this study was an adult critically ill patient diagnosed by sepsis. Blood lactate level and blood gas analysis improvement is the outcome of the study. The clinical question of this study was "could the thiamine supplementation improve the blood lactate and blood gas analysis in adult critically ill patient with sepsis?

P : adult critically ill patient with sepsis
I : thiamine supplementation and/or thiamine level
C : not-supplemented by thiamine and/or thiamine deficient
O : Lactate clearance/acidosis

Methods

We conducted evidence-based case report with search strategy, critical analysis, and synthesis. Searching was done on PubMed, ProQuest, and Scopus on 26 September 2020, 27 September 2020, and 28 September 2020 respectively. Author used keywords ("thiamine" OR "B1") AND (("critically ill" OR "critical illness") AND "sepsis") on ProQuest and Scopus; and (("Critical Illness"[Mesh]) AND ("Sepsis"[Mesh])) AND ("Thiamine"[Mesh]) on PubMed. Authors selected articles using inclusion and exclusion criteria. Inclusion criteria were: (1) randomized clinical trial or prospective/retrospective study; (2) population of adult critically ill patient with sepsis; (3) thiamine supplementation or level as intervention or indicator; (4) blood lactate and/or blood gas analysis as outcome; (5) written in English. Authors excluded review articles.

Selected articles were appraised using critical appraisal tools from Center for Evidence-Based Medicine (CEBM) University of Oxford, with any discrepancy discussed further for final decision on appraisal result.[8] Appraised studies were extracted on its author(s), study year, design, location, age, sample size, intervention and control treatment, aim of study, primary endpoint, level of evidence according to CEBM Oxford, and outcomes.[9] Studies were synthesized further for results, discussion, and concluded by five authors.

Results

We found total 124 studies after hit on PubMed, Scopus, and ProQuest combined which could be seen on Figure 1. After hand searching and elimination of duplicated study, we found 5 studies eligible for full text assessment and screening of methods and results. Finally, we found 3 studies eligible for this study as one study assessed effect of vitamin B1 together with vitamin C and n-acetylcysteine (Bedreag, *et al*) and one study assessed effect of vitamin B1 together with vitamin C (Yoo, *et al*).[10–15] Therefore, included studies after selection process were studies by Byerly, *et al*; Donnino, *et al*; and Woolum, *et al*.[10–12]

Both studies were appraised, and both studies were eligible and qualified in terms of validity and applicability which could be seen on Table 1. Importance of studies were qualified as the results shown significance and relationship over time. It is known from the study outcome that thiamine supplementation or sufficiency could give protective effect towards lactic acidosis ($p<0.05$). In addition, study by Woolum, *et al* suggested that thiamine could reduce 28-day mortality by 0.67 times (95% CI 0.49–0.91). Byerly, *et al* also suggested that thiamine supplementation alone or with vitamin C were associated with increased in-hospital survival and lactate clearance which could be seen alongside study characteristics in Table 2.

Discussion

Studies qualities were shown in a good condition after critical appraisal. All three studies were sufficient in validity, importance, and applicability.[10–12] Therefore, findings in these studies should be brought into consideration for further practice. However, two studies could not be assessed for follow up as they did retrospective approach, thus follow up is not applicable in this case.[10,12] Study importance was described on study charateristics.

Critically ill patients with shock tend to develop thiamine deficiency as result of low or nil intake, increased oxidative stress in mitochondria, and other existing comorbidities which could provoke rapid deterioration of thiamine supply.[12] Sepsis could increase metabolic requirement due to rapid breakdown of human energy resources and induce inadequate nutrition uptake, thus leading to thiamine deficiency.[13] Acute stress will mobilize building blocks of human in-order to response stressor. In addition, acute stress will suppress feeding pattern and gastric absorption, thus inducing thiamine deficiency.[14] On the other hand, critically ill patients are subject to limited uptake, impaired renal function, and dramatic elevation of oxidative stress, thus lead to thiamine deficiency.[15]

It is known that 10% of critically ill patient with sepsis present with thiamine deficiency on admission, and 10% more will present 72 hours after admission.[11] Thiamine plays a role in Kreb's cycle as it serves as cofactor of pyruvate dehydrogenase and alpha ketoglutarate dehydrogenase. Thus, depleted thiamine level clearly disrupts aerobic metabolism process which inhibit oxidative metabolism and ATP production. These cascades could be manifested as lactic acidosis, hypotension, and death.[12] Sufficient thiamine level by thiamine supplementation could be an answer for this problem as one study by shown that thiamine treatment could improve probability of lactate clearance by 1.307 times (95% CI 1.002–1.704).[12] This coherent with another study that thiamine administration only gave positive impact towards lactate clearance and its impact could be emphasized by vitamin C co-supplementation.[10] This mechanism gave better prognosis for the patient, well-defined by mortality rate. It is known that thiamine supplementation could reduce in-hospital mortality rate by 0.710 times (95% CI 0.550–0.930) 28-day mortality rate by 0.666 times (95% CI 0.490–0.905).[10,12] In addition, co-supplementation with vitamin C could reduce in-hospital mortality 0.223 times (95% CI 0.069–0.735).[12] Moreover, combination of vitamin C and thiamine supplementation yielded positive relation towards lactate clearance and patient's prognosis ($p<0.05$).[16–17] Based on those findings and the fact that vitamin C is a potent antioxidant and anti-inflammatory agent, vitamin C supplementation along with thiamine administration could be considered or studied further for better evidence. However, further studies are recommended to determine vitamin C effect adjunct to thiamine supplementation on critically ill patients with sepsis.

However, there is an anomaly pattern in patient with liver injury (ALT >240 IU/L).[10] Patient with liver injury had generous level of both thiamine and lactate. Dancy, *et al* suggested another finding that alcoholic patients tend to have higher thiamine level.[18] This could be explained by pathophysiologic explanation that patient with liver failure has incapability to store thiamine and to process thiamine as result of mitochondrial damage in liver. Therefore, liver damage will result in breakdown of thiamine-containing complexes which off-loaded in serum circulation. Patient with liver damage also has trouble of lactate metabolism. This explain why patient with liver damage did not benefit much from thiamine supplementation and even worsen his/her lactate status.[10] Another thing to be noted is gender response towards thiamine supplementation. Woolum *et al* suggested that female are favorable responders compared to male, which also means that female is more prone towards thiamine deficiency. Therefore, beside pregnancy and lactation process, there are several things should be taken into notes when female develop thiamine deficiency such as inflammatory response and hypervolemia. This should be considered as hypothesis and taken into future research on thiamine and septic shock on critically ill patients

This is evidence-based study that determine relationship of thiamine deficiency or supplementation with clinical outcome of ICU patients with sepsis such as mortality, lactate

clearance, and others that could contribute to patient's prognosis. However, this study did not determine individual response towards thiamine supplementation. Therefore, it is recommended to do multicenter randomized control trial on thiamine supplementation and factors contributing into therapeutic response.

Conclusion

Thiamine supplementation to maintain thiamine sufficiency was essential in critically ill patients with sepsis as it could improve patient's lactate clearance hence improving survival and prognosis. Therefore, maintenance of thiamine level is recommended to prevent deterioration of clinical performance of critically ill patient; and thiamine administration is recommended for critically ill patient with sepsis. It is also recommended to make further studies on thiamine supplementation on critically ill patients with sepsis with special characteristics such as pregnancy, geriatric, and liver disease to improve applicability of this report. Thiamine supplementation with other substances should be studied further to improve importance of this study.

Table 1. Critical appraisal of selected studies using critical appraisal tools for follow-up study from CEBM Oxford.[8]

Author (Year)	Validity			Applicability		
	Representative sample	Follow-up	Blind' fashion	Adjustment	Patient similarity	Clinically important
Byerly, *et al* (2020)	+	N/A	+	+	+	+
Donnino, *et al* (2010)	+	+	+	+	+	+
Woolum, *et al* (2018)	+	N/A	+	+	+	+

Table 2. Characteristic of selected studies[9]

Author (Year)	Study Design	Location	Age	Sample Size	Follow up	Follow up rate	Aim	Primary Endpoint	Level of Evidence[9]	Outcome
Byerly, *et al* (2020)[10]	Retrospective cohort	Miami	58.1±13.6	146,687	N/A	N/A	Evaluate effect of vitamin C and thiamine on mortality and lactate clearance in intensive care unit patients.	In-hospital mortality	2b	(1) Thiamine independently associated with in-hospital survival (AOR=0.71; 95% CI 0.55–0.93); (2) Thiamine was positively related with lactate clearance (AOR=1.50; 95% CI 1.22–1.96); (3) Combination of vitamin C and thiamine supplementation were linked with survival (AOR=0.335; 95% CI 0.130–0.865) and lactate clearance (AOR=1.85; 95% CI 1.05–3.24)
Donnino, *et al* (2010)[11]	Prospective cohort	Boston	34–61	60	0, 24, 48, 72, 162 hours	100%	Determine thiamine deficiency's prevalence in ICU patients with sepsis so that association between thiamine levels and lactic acidosis could be determined.	Lactic acid levels	1b	(1) Positive correlation between thiamine and liver transaminase (p=0.020); (2) Positive correlation between liver transaminase and lactic acidosis (p=0.030); (3) Thiamine was associated negatively with lactic acid level in patients with healthy liver (p=0.014).
Woolum, *et al* (2018)[12]	Retrospective cohort	Kentucky	43–61	369	N/A	N/A	Determine association between thiamine administration in septic shock and clinical manifestations such as lactate clearance.	Lactate clearance	2b	(1) Thiamine supplementation linked positively with improved chance of lactate clearance (HR = 1.307; 95% CI 1.002–1.704); (2) Thiamine supplementation linked positively with reduced 28-day mortality (HR=0.666; 95% CI 0.490–0.905)

Abbreviations: N/A=Not Applicable

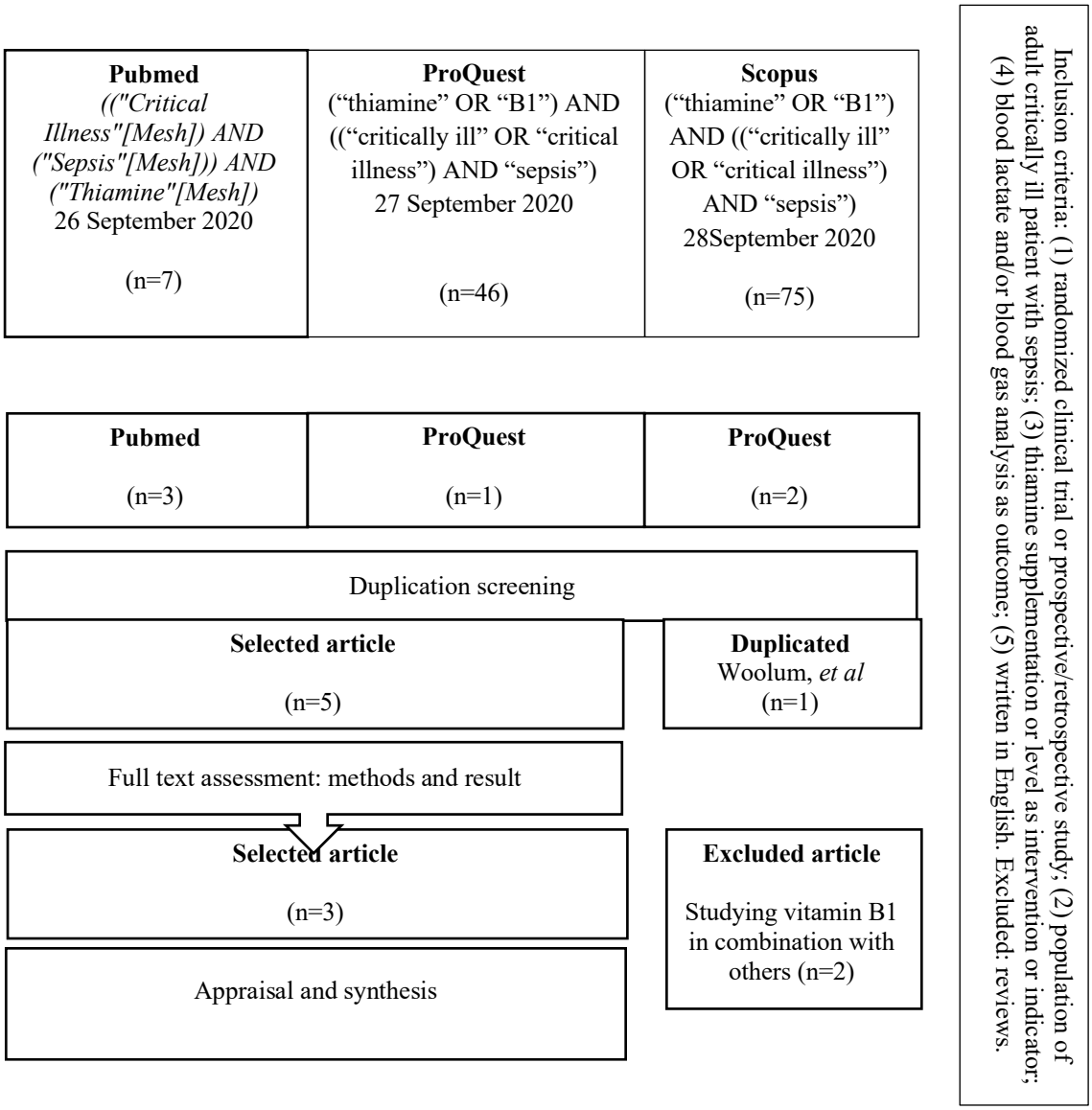

Figure 1. Literature searching process

Conflict of Interest

Authors declare there was no conflict of interest regarding this study.

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